

Contribution of Respiratory Disease to Nonrespiratory Mortality Associations with Air Pollution

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Many time series studies have found that individuals with primary cardiac conditions were susceptible to the adverse effects associated with increased ambient particle levels. However, the mechanism(s) of these associations is not yet understood. In this study, we evaluate whether individuals with nonrespiratory primary causes of death who also had contributing respiratory causes listed on their death certificates were more affected by air pollution, as compared with those not having contributing respiratory conditions. Short-term associations between ambient particulate matter (10 μm or less in aerodynamic diameter) and mortality were modeled in New York City for the years 1985–1994. It was observed that among those 75 years or more, those with contributing respiratory disease had higher relative risks (95% confidence intervals) calculated per interquartile range, as compared with those without contributing respiratory disease for both circulatory deaths (relative risk = 1.066 [1.027–1.106] versus 1.022 [1.008–1.035]) and cancer deaths (relative risk = 1.129 [1.041–1.225] versus 1.025 [1.000–1.050]). However, this pattern of association was not observed for those who were less than 75 years old. The results of this study suggest that past studies may have underestimated the role of respiratory disease in pollution-mortality associations, especially among older adults.

Keywords: particulate matter; circulatory mortality; air pollution

Despite the number of epidemiologic time series studies that have observed associations between ambient particulate matter (PM) levels and circulatory mortality (1) and morbidity (2, 3), the mechanism(s) behind these associations is not yet understood. It is biologically plausible that inhalation of ambient PM can have harmful effects on the lung. Controlled exposure studies in humans have shown that exposure to concentrated particles of ambient origin have resulted in pulmonary inflammation and lung injury in healthy adults (4–6). Harmful effects on the lung could adversely affect those with pre-existing circulatory conditions. For instance, it is possible that increased lung permeability can allow chemical mediators produced in the lungs or particles breathed into the lungs to enter the circulation and have a systemic effect or a direct effect on the myocardium (7). Seaton and colleagues (8) hypothesized that ultrafine particle-induced alveolar inflammation could cause the release of mediators that increase blood coagulability. Studies have shown that increased blood coagulability or viscosity is a risk factor for cardiovascular deaths (9, 10), and a few researchers have

found associations between increased plasma viscosity and ambient PM (11, 12) and concentrated ambient PM (5). Indeed, if the air pollution-induced effect on the lungs is severe, deaths with a respiratory condition noted somewhere on the death certificate should be associated with the short-term fluctuations in ambient PM. Thus, looking only at the primary or the underlying cause of death listed on the death certificate may mask the involvement of respiratory disease in cardiac death associations.

Our objective in this work was, therefore, to determine whether deaths with secondary respiratory conditions were more strongly associated with ambient particle levels when compared with those deaths without a secondary respiratory condition. Because advanced age may also modify the association, due to increased severity and complexity of the underlying disease, we also examined whether the air pollution effect estimates for deaths with or without contributing respiratory disease were modified by age by comparing the effect in an older group (75 years old or more) versus a younger group (less than 75 years old). To assess the short-term associations of air pollution with mortality, Poisson time series analysis was used adjusting for weather effects, day of the week patterns, and seasonal influences on day of death. Although causes of death listed on the death certificate are subject to misclassification errors, particularly when trying to separate respiratory and circulatory causes of death, this is the best available source of information regarding deaths that occur in the general population.

Analyses were conducted for New York City, including Bronx, Kings, New York, Queens, and Richmond counties, for the years 1985–1994. The large population (approximately 7.3-million people) increased the power to detect associations with the smaller mortality subcategories. Single- and two-pollutant regression models, with PM 10 μm or less in aerodynamic diameter (PM₁₀) and gaseous copollutants, were conducted. Preliminary results from this study have been presented in the form of an abstract (13).

METHODS

Daily deaths for those who resided and died in New York City were aggregated for January 1, 1985, through December 31, 1994. Death counts in which the primary cause of death was circulatory (*International Classification of Diseases*, 9th edition, code: 390–459) or cancer (*International Classification of Diseases*, 9th edition, code: 140–239) were aggregated into a daily time series. In addition, daily counts were aggregated for each primary cause of death category with or without respiratory (*International Classification of Diseases*, 9th edition, code: 460–519) contributing causes of death. To determine whether air pollution associations were modified by age, the effect estimates for those less than 75 years old (the median of the age distribution of deaths) and those 75 years old or more were also considered.

Air pollution data were obtained from the Environmental Protection Agency's Aerometric Information Retrieval System. Daily 24-hour average PM₁₀ were available for 585 days (every 6th day) after taking multiple sites' averages. The every 6th-day sampling prevents any potential day of the week effect. Daily (24 hour) averages for the gaseous pollutants, such as ozone (O₃), carbon monoxide (CO), sulfur dioxide,

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TABLE 1. PERCENTILE DISTRIBUTION (5TH TO 95TH) OF DAILY DEATHS (BY CAUSE OF DEATH CATEGORY)

All Ages	Mean Number of Deaths Per Day	Percentiles				
		5	25	50	75	95
Total	179.42	148	165	177	193	216
Respiratory	13.91	7	11	13	17	22
Circulatory	87.21	67	77	86	95	112
with respiratory	8.44	3	6	8	11	15
without respiratory	78.77	60	70	77	86	101
Cancer	38.50	28	34	38	43	49
with respiratory	3.09	0	2	3	4	6
without respiratory	35.41	26	31	35	40	45
Age less than 75						
Total	95.82	77	87	95	104	116
Respiratory	5.74	2	4	5	7	10
Circulatory	33.77	23	29	33	38	47
with respiratory	2.83	0	2	3	4	6
without respiratory	30.94	20	26	30	35	43
Cancer	24.39	16	21	24	28	33
with respiratory	1.89	0	1	2	3	4
without respiratory	22.49	15	19	22	26	31
Age 75 or more						
Total	83.61	65	74	82	91	106
Respiratory	8.05	3	6	8	10	14
Circulatory	53.35	39	46	52	59	71
with respiratory	5.61	2	4	5	7	10
without respiratory	47.75	35	41	47	53	64
Cancer	14.10	8	11	14	17	21
with respiratory	1.20	0	0	1	2	3
without respiratory	12.90	7	10	13	15	19

Both primary causes of death and primary causes of death with or without contributing respiratory causes are shown for New York City for the years 1985–1994.

and nitrogen dioxide (NO₂), were available for more than 96% of the entire study period or 3,500 days.

Weather variables (temperature and relative humidity) for New York LaGuardia International Airport from the National Climatic Data Center were extracted from the EarthInfo (Boulder, CO) compact disks.

Short-term associations between air pollution and mortality were modeled using Poisson Generalized Additive Models (14), adjusting for seasonal trends and weather effects and allowing for overdispersion in the mortality data (further details are in the online supplement). To ensure that the estimated coefficients converge appropriately, the convergence precision and maximum number of iterations, for both the local scoring and backfitting algorithms, were set to 10⁻¹⁴ and 1,000, respectively, as recommended by Dominici and colleagues (15).

To focus on short-term health effects only, the pollution variables were detrended by regressing each pollutant on a smooth function of time (approximately 3 weeks and longer period) and taking the residuals. In effect, this process filters out the longer term trend, including seasonal cycles, leaving only the shorter-term patterns in the series. Specific causes of death, as well as deaths both with and without contributing respiratory causes, were analyzed as separate series. Analyses were restricted only to days when averaged PM₁₀ values were available. Positive effect estimates for the causes of death occurred on either the same day or a 1-day lag (results not shown). Thus, for brevity in presenting these results, pollution variables were added to the model using a 0- to 1-day averaging time. Relative risk estimates were calculated per interquartile range of the raw pollutant, to make comparisons across pollutants.

To compare the level of risk between the two cause-of-death groups (i.e., circulatory deaths with and without contributing respiratory causes), a *t*-test assuming unequal variances of the two populations was used. Because our prior hypothesis was that contributing respiratory disease might increase, but not decrease the effect of air pollution, one-way *p* values were examined for comparison purposes. Two-pollutant models, including PM₁₀ and each of the gaseous pollutants, were also conducted. S-Plus software (Mathsoft Inc., Cambridge, MA) was used to conduct all analyses.

RESULTS

Descriptive Statistics

The distributions of the daily counts for each of the mortality subcategories for the years 1985–1994 are shown in Table 1. Although deaths in which the primary cause was a circulatory condition account for approximately half of all deaths, primary respiratory deaths only account for approximately 8% of all deaths. For all ages combined, pneumonia (*International Classification of Diseases*, 9th edition, code: 480–487) and chronic obstructive pulmonary diseases (COPDs) (*International Classification of Diseases*, 9th edition, code: 490–496) made up approximately 83% of all primary respiratory deaths.

The major primary circulatory causes of death (see Table E1 in the online supplement) were chronic ischemic heart disease (coronary atherosclerosis) and acute myocardial infarction. For the two age groups, the breakdown of major circulatory diagnoses was similar to that for all ages combined, except that for those 75 years old or more, there were more individuals diagnosed with chronic ischemic heart disease (coronary atherosclerosis) and congestive heart failure.

When deaths were divided into those with contributing respiratory causes versus those without, those who had contributing respiratory causes only made up approximately 10% of deaths for both primary cancer and circulatory deaths (Table 1). For both circulatory and cancer deaths, approximately 70% of the contributing respiratory conditions diagnosed were either pneumonia or COPD. Among those 75 years old or more who died of a circulatory condition, pneumonia was mentioned as a contributing cause of death approximately 43% of the time, whereas for those less than 75 years old, pneumonia was mentioned as a contributing cause approximately 26% of the time.

The distributions of daily weather and pollution variables during the study period are shown in Table 2. The Pearson cor-

TABLE 2. PERCENTILE DISTRIBUTION OF DAILY WEATHER AND POLLUTION VARIABLES FOR NEW YORK CITY FOR THE YEARS 1985–1994

Variable	Mean	Percentiles				
		5	25	50	75	95
PM ₁₀ , µg/m ³	33.27	15.57	22.67	30.83	40.83	61.93
O ₃ , ppb	21.59	7.00	13.15	19.00	27.60	44.97
CO, ppm	2.45	1.38	1.80	2.27	2.97	4.04
SO ₂ , ppb	14.64	5.00	8.18	12.38	18.40	32.62
NO ₂ , ppb	40.55	25.33	32.67	39.00	46.67	62.00
Temperature, °F	55.36	28.00	42.00	56.00	71.00	80.00
Relative humidity, %	64.39	42.00	53.00	63.00	75.00	90.00

Definition of abbreviations: CO = carbon monoxide; NO₂ = nitrogen dioxide; O₃ = ozone; PM₁₀ = particulate matter 10 µm or less in aerodynamic diameter; ppb = parts per billion; ppm = parts per million; SO₂ = sodium dioxide.

relation coefficients for the weather and pollution variables with and without seasonal influences are shown in Table E2 (*see* the online supplement). The pollutants tend to be moderately correlated, regardless of whether the variables are detrended. Of all the pollutants considered, O₃ was the pollutant least correlated with PM₁₀ after detrending.

Analyses by Cause and Age

The regression results indicate that, generally, both primary circulatory and cancer deaths with contributing respiratory causes tended to have greater pollutant effect estimates than those without contributing respiratory causes, for all pollutants considered. Effect estimates and 95% confidence intervals for PM₁₀ are shown for all mortality outcomes in Table 3. For all ages combined, with the exception of O₃ and NO₂, cancer deaths with contributing respiratory causes had larger pollutant effect estimates as compared with cancer deaths without contributing respiratory causes ($p < 0.10$) (*see* Figure E1A in the online supplement). For circulatory deaths (Figure E1B), the effect estimates were greater for deaths compared with those without contributing respiratory causes, for all pollutants considered ($p < 0.10$), except O₃.

When the data were stratified by age, among those less than 75 years old, there were no significant differences in effect estimates observed based on the presence or absence of contributing respiratory disease, whereas among those 75 years old or more, having a contributing respiratory condition was associated with a greater pollutant effect estimate. Effect estimates and 95% confidence intervals for PM₁₀ are shown for each age group in Table 3. For those less than 75 years old, the results for all pollutants are shown in Figure 1. Primary cancer deaths (without stratification into those with or without contributing respiratory causes) were not associated with any of the pollutants except O₃ and NO₂ (Figure 1A), whereas primary circulatory deaths were associated with all pollutants except O₃ (Figure 1B). Although deaths with contributing respiratory causes generally had larger effect estimates for both cancer and circulatory deaths, none of the estimates were significantly different from one another. In the older age group (75 years old or more), primary cancer and circulatory deaths were associated with all pollutants (*see* Figure 2). Similar to the results for all ages combined, larger effects were observed for cancer deaths with contributing respiratory causes ($p < 0.05$), with the exception of O₃ and NO₂ (Figure 2A). Among those for whom the primary cause of death was due to a circulatory condition (Figure 2B), the presence of a contributing respiratory condition was found to increase the temporal association between death and ambient pollution levels, for all pollutants ($p < 0.05$), except O₃.

To determine whether those with chronic or infectious respi-

ratory diseases were more strongly associated with ambient pollution levels, we also considered circulatory and cancer deaths with, versus without, contributing pneumonia or COPD. Because the associations were strongest for those 75 years old or more, these results are shown for PM₁₀ in Table 3. The results indicate that those with secondary pneumonia have a greater pollutant-associated risk of premature death as compared with those with secondary COPD, particularly when the primary cause of death is cancer.

Effect estimates for PM₁₀ and the gaseous pollutants were each generally attenuated in two-pollutant models versus single-pol-

TABLE 3. PARTICULATE MATTER RELATIVE RISK CALCULATED FOR PERCENTILE DISTRIBUTION INCREMENTS (INTERQUARTILE RANGE) OF THE RAW POLLUTANT FOR SPECIFIC CAUSES OF DEATH IN NEW YORK CITY USING MORE STRINGENT CONVERGENCE CRITERIA FOR THE GENERALIZED ADDITIVE MODELS

Mortality	RR	95% CI
All Ages		
Cancer	1.014	(1.000, 1.029)
without respiratory	1.011	(0.996, 1.026)
with respiratory	1.051	(0.998, 1.107)
Circulatory	1.025	(1.014, 1.035)
without respiratory	1.022	(1.012, 1.033)
with respiratory	1.054	(1.022, 1.086)
Age less than 75		
Cancer	1.003	(0.985, 1.021)
without respiratory	1.002	(0.983, 1.022)
with respiratory	1.009	(0.943, 1.078)
Circulatory	1.027	(1.012, 1.043)
without respiratory	1.027	(1.011, 1.043)
with respiratory	1.033	(0.980, 1.089)
Age 75 or more		
Cancer	1.033	(1.009, 1.058)
without respiratory	1.025	(1.000, 1.050)
with respiratory	1.129	(1.041, 1.225)
without pneumonia	1.026	(1.002, 1.050)
with pneumonia	1.183	(1.058, 1.323)
without COPD	1.032	(1.008, 1.057)
with COPD	1.008	(0.849, 1.197)
Circulatory	1.025	(1.012, 1.038)
without respiratory	1.022	(1.008, 1.035)
with respiratory	1.066	(1.027, 1.106)
without pneumonia	1.023	(1.010, 1.036)
with pneumonia	1.078	(1.018, 1.141)
without COPD	1.025	(1.012, 1.038)
with COPD	1.058	(0.991, 1.130)

Definition of abbreviations: CI = confidence interval; COPD = chronic obstructive pulmonary disease; PM₁₀ = particulate matter 10 µm or less in aerodynamic diameter; RR = relative risk.

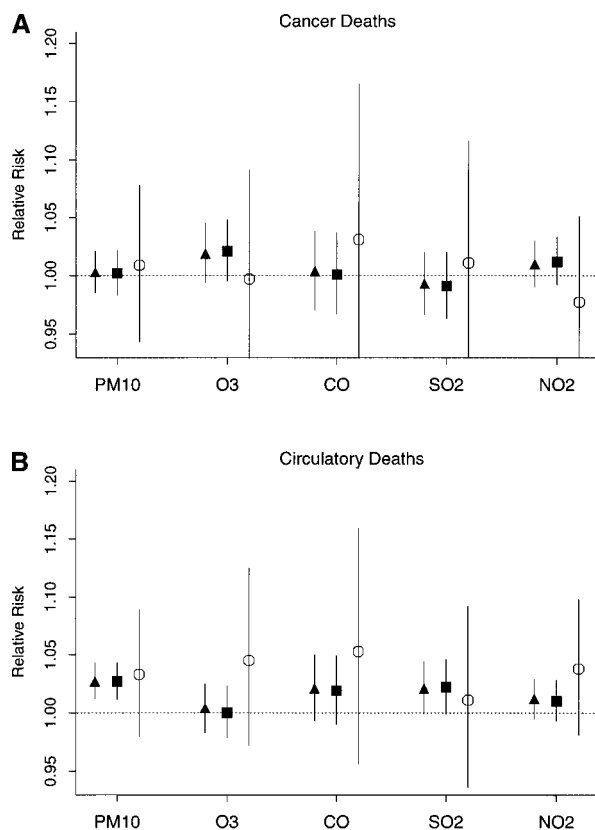


Figure 1. Relative risks were calculated per 25th to 75th percentile distribution increment (interquartile range) of the raw pollutant for primary cancer (A) and circulatory (B) deaths with and without contributing respiratory causes (age less than 75 years). Error bars represent the 95% confidence intervals for each risk estimate. Triangles = primary cause of death; squares = deaths without contributing respiratory causes; circles = deaths with contributing respiratory causes.

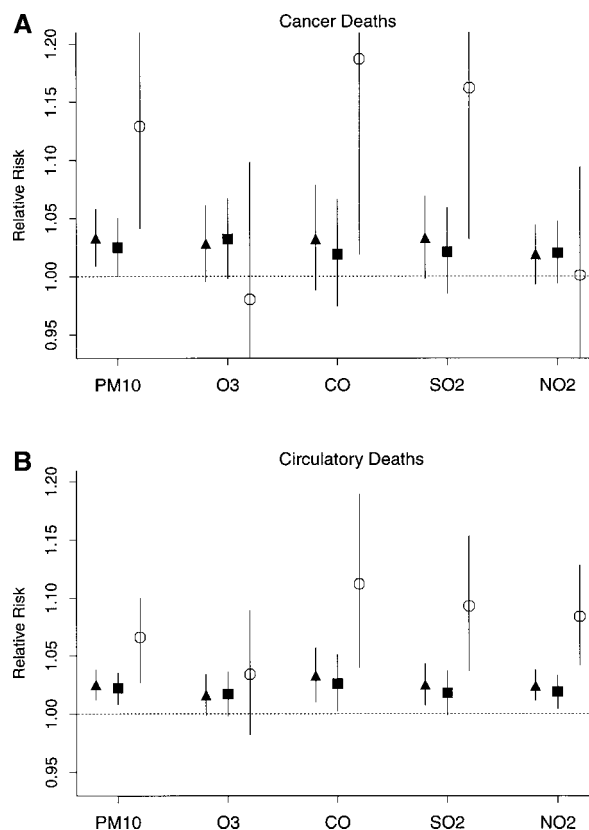


Figure 2. Relative risks were calculated per 25th to 75th percentile distribution increment (interquartile range) of the raw pollutant for primary cancer (A) and circulatory (B) deaths with and without contributing respiratory causes (age 75 years or more). Triangles = primary cause of death; squares = deaths without contributing respiratory causes; circles = deaths with contributing respiratory causes.

lutant models. However, the magnitude and direction of the differences between the effect estimates for deaths with, versus without, contributing respiratory causes remained the same for circulatory and cancer deaths and were within the 95% confidence intervals of the original single-pollutant estimates for all age strata considered. Among those 75 years old or more, the PM₁₀ estimates in the two-pollutant models were still greater for the primary cause of death with contributing respiratory causes as compared with the estimates for those deaths without contributing respiratory causes (Figures 3 and 4). However, when PM₁₀ and NO₂ were included in the same model, the PM₁₀ estimate for circulatory deaths with and without contributing respiratory causes became comparable (Figure 4B). Inclusion of PM₁₀ in the model decreased the gaseous pollutant effect estimates, although the relationship between the estimates for deaths with or without secondary respiratory disease remained the same.

Although the more stringent convergence criteria for the Generalized Additive Models were used to avoid potential bias in the estimated coefficients, Dominici and colleagues (15) suggested that the SEs may still be underestimated. The authors further suggest that both the β and the SE would be less biased if Generalized Linear Models (with parametric methods such as regression splines or natural cubic splines) were used to model potential nonlinear relationships. Therefore, Generalized Linear Models with parametric smooth functions (natural cubic splines) were also considered and presented in the online supplement

(Table E3). As expected, the SEs for the effect estimates were generally larger for the Generalized Linear Model compared with the Generalized Additive Model (e.g., for PM₁₀ effect estimates, SEs were 6–15% larger depending on the mortality category considered). However, the conclusions of this study were not altered based on whether Generalized Additive Models or Generalized Linear Models were used to model the association.

In addition to these analyses, nondetrended or raw pollution variables were included in the mortality regression model to determine the sensitivity of the results to detrending of the pollutant. Generally, the results were not found to be sensitive to whether or not the pollutant was detrended, with the possible exception of CO, which had larger effect estimates for the detrended compared with the raw pollutant, particularly for deaths with contributing respiratory causes (all ages combined).

DISCUSSION

The results of this study suggest that in individuals whose primary cause of death was a nonrespiratory condition (such as circulatory or cancer), those also having a contributing respiratory condition, particularly an infectious condition, were more affected by the adverse effects associated with increased ambient air pollution levels. Past time series studies that have considered only the primary cause of death have generally found that the relative risk associated with ambient air pollution was larger for respiratory deaths than for circulatory deaths (16, 17). These

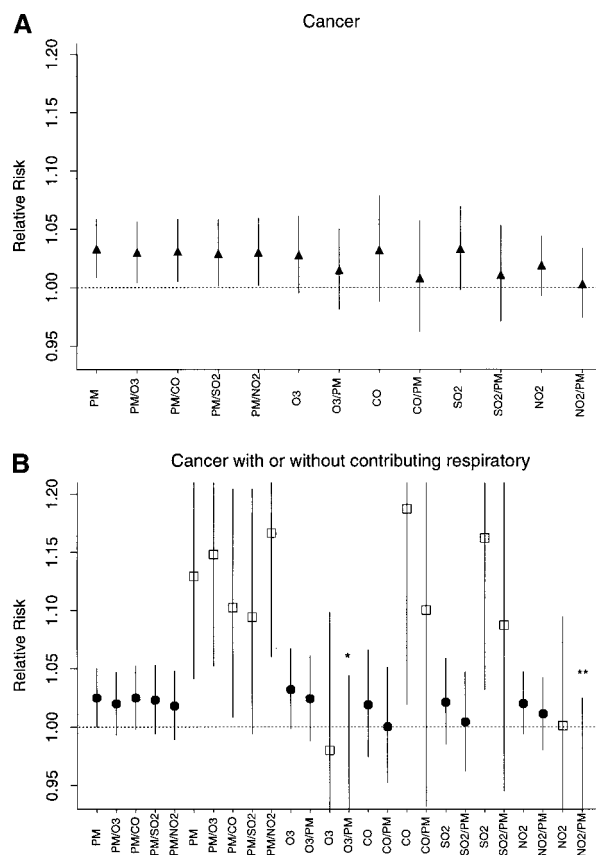


Figure 3. Relative risks for the two-pollutant models were calculated per 25th to 75th percentile distribution increment (interquartile range) of the raw pollutant for primary cancer deaths (A) and primary cancer deaths with and without contributing respiratory causes (B) among those 75 years old or older. Notation on the x axis indicates the effect estimate for each pollutant in single and two-pollutant models (e.g., PM/O₃ represents the PM₁₀ estimate given that O₃ was included in the model, and PM represents the PM₁₀ estimate in the single-pollutant model). *Triangles* = primary cause of death; *circles* = deaths without contributing respiratory causes; *squares* = deaths with contributing respiratory causes. *Relative risk = 0.924. **Relative risk = 0.923.

results are consistent with the hypothesis that the presence of a coexisting respiratory condition could increase the association between circulatory causes of death and days with higher air pollution. Although death certificates that list a respiratory condition as the primary cause of death make up approximately 8% of total nonaccidental deaths in New York City, primary circulatory or cancer deaths that list respiratory disease as a contributing cause of death make up some 6.5% of total deaths. Because both circulatory and cancer deaths with contributing respiratory causes were significantly associated with ambient PM levels, consideration of contributing causes roughly doubles the number of deaths involving respiratory disease that are potentially at risk for adverse effects caused by exposure to ambient PM, over analyses that only consider deaths with respiratory disease as the primary cause of death.

At least one study has examined how the associations between air pollution and health outcomes are modified with the presence or absence of contributing respiratory diseases. Zano-betti and colleagues (18) analyzed hospital admissions data for Chicago, IL, during the years 1986–1994 and, in agreement with the results observed in this study, found that those with a primary

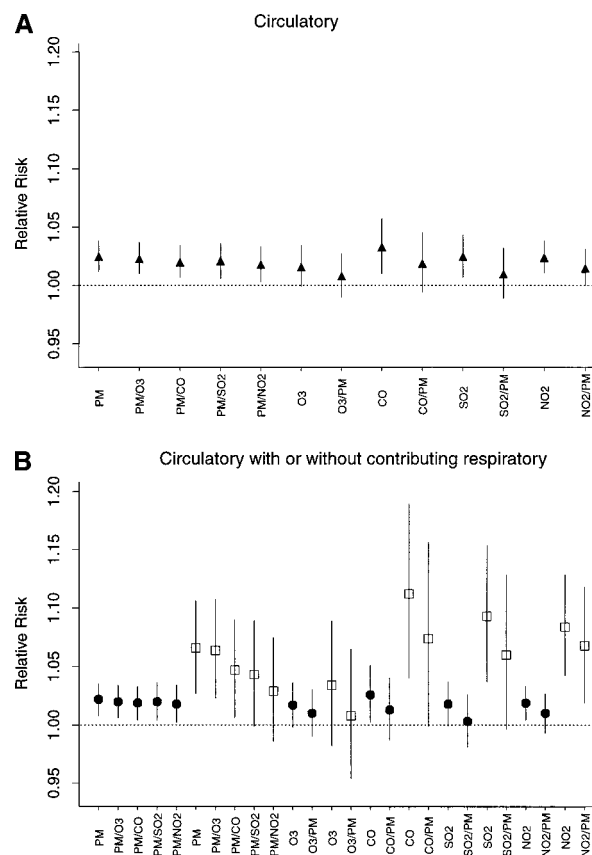


Figure 4. Relative risks for the two-pollutant models were calculated per 25th to 75th percentile distribution increment (interquartile range) of the raw pollutant for primary circulatory deaths (A) and primary circulatory deaths with and without contributing respiratory causes (B) among those 75 years old or more. *Triangles* = primary cause of death; *circles* = deaths without contributing respiratory causes; *squares* = deaths with contributing respiratory causes.

circulatory condition that had contributing respiratory causes had a greater association with premature death on days with increased air pollution compared with those that had no contributing respiratory causes.

Past morbidity (3, 19) and mortality (20, 21) studies have found that the effect of air pollution was more pronounced in the older population (65 years old or more). It has also been observed that the effect of air pollution was modified by age among the older population in that those older than 75 years had a greater risk of pollution-related death compared with those who were younger (22, 23). In this study, it was found that among individuals 75 years old or more, the presence of contributing respiratory disease significantly increased the association with ambient PM for those with a primary circulatory or cancer condition. However, for those less than 75 years old, no difference in effect was observed based on the presence of contributing respiratory causes for cancer or circulatory deaths. The level of sensitivity in the two groups may have been influenced by certain characteristics of each group. For instance, among those less than 75 years old, primary cancer deaths were not associated with most of the pollutants considered (Figure 1A) so that observing no difference in effect estimates based on the presence of contributing respiratory causes was not entirely unexpected. In addition, those more than 75 years of age had more cases of congestive heart failure and chronic ischemic heart disease (coronary

atherosclerosis), as well as a higher percentage of circulatory deaths with pneumonia mentioned as a contributing cause of death (43% versus 26% for those less than 75 years). The observed increased susceptibility to air pollution effects with age may be due to a combination of more severe circulatory disease, as illustrated by higher percentages of chronic ischemic heart disease and congestive heart failure, together with a higher proportion of cases with pneumonia as a coexisting respiratory condition.

It has been hypothesized that those with chronic respiratory conditions such as COPD, who have poor gas exchange in certain portions of their lungs, may be particularly sensitive to short-term decreases in oxygen saturation of the blood, which could have a potential adverse effect on those with pre-existing heart conditions (24, 25). However, Pope and colleagues (26) in a panel study of older individuals found that arterial oxygen saturation was not significantly decreased with exposure to increased levels of ambient PM. In this study, it was observed that among those 75 years old or more, there was no observed difference in effect among those with versus without contributing COPD, although COPD was frequently mentioned as a contributing cause (e.g., 32% for those greater than 75 years old). In contrast, the risk estimate was significantly greater among those with compared with those without contributing pneumonia, and pneumonia was more commonly mentioned as a contributing cause when the primary cause of death was a circulatory condition.

In addition to contributing respiratory disease increasing the air pollution associated risk, it was observed in this study that circulatory deaths without contributing respiratory causes were consistently positive and significantly associated with ambient air pollution. This suggests that exposure to ambient air pollution may also have an effect on the circulatory system or the heart over and above those deaths involving a respiratory condition. There is some evidence to suggest that those with pre-existing circulatory conditions can be sensitive to inhaled PM in the absence of pre-existing respiratory conditions. Pope and colleagues (26), in a panel study of older patients, found positive associations between heart rate and ambient PM among patients with cardiac conditions that had no history of respiratory disease. Among those with more severe cardiac conditions (manifested more than 10 beats per minute above the average pulse rate for a given individual during the study period), the most positive association between heart rate and ambient PM was for those with cardiac conditions and no history of respiratory disease. Several other studies have found that changes in indicators of autonomic instability, as measured by deviations in heart rate or heart rate variability, were associated with ambient PM (27–29) and environmental tobacco smoke (30), although patients with acute respiratory infections were excluded from these studies.

The role of respiratory disease in air pollution-related cardiovascular deaths may be larger than estimated in this study. There may not be a distinct separation between circulatory deaths with and without contributing respiratory causes, as circulatory and respiratory diseases are closely related physiologically, as well as due to the potential for underreporting of contributing causes of death in general, and particularly for contributing respiratory causes (31). Previous studies have compared the level of agreement on the primary cause of death reported on the death certificate and autopsy (32–34) and on review of medical records (35, 36). Based on these studies, the upper limit of respiratory disease misdiagnosed as circulatory disease can be as large as 33%, and the upper limit of circulatory disease that can be misdiagnosed as respiratory disease can be as large as 5%. Because respiratory disease, both as a primary and contributing cause of death, has effect estimates generally twice as great as those for circulatory conditions, it seems unlikely that a 5% misdiagnosis rate of circulatory disease as respiratory disease could inflate

the respiratory effect estimate. Therefore, realistic levels of misclassification between circulatory and respiratory categories would not be expected to alter the conclusions of this study. Because there is less potential for misdiagnosis between cancer and circulatory or respiratory diseases (32–36), the interpretations and conclusions based on the subcategories involving cancer are less hampered by concerns about misdiagnosis.

In this study, for all pollutants considered (with the exception of O₃), larger effect estimates were observed for deaths with as compared with those without contributing respiratory causes. These results were generally robust to the inclusion of a second pollutant in the model. The only exception being that the PM₁₀ effect estimates for circulatory deaths with or without contributing respiratory causes became comparable after the inclusion of NO₂ in the model (Figure 4). However, these individual estimates may be biased, as PM₁₀ and NO₂ have the highest correlation ($r = 0.73$) among all of the pollutants, and thus, it is difficult to ascribe effects to one or the other of these pollutants.

The pattern of effects for O₃ was not generally consistent with that for the other pollutants. For cancer deaths, no differences in effect estimates were observed for O₃ based on the presence of contributing respiratory disease, for all age strata considered. Although circulatory deaths with contributing respiratory causes had larger effect estimates, as compared with those without contributing respiratory causes for those less than 75 years old, as well as for those 75 years old or more, none of these effects were significantly different from one another. Ozone was not highly correlated with PM₁₀ or any of the other gaseous pollutants (Table E2) and often remained significant in two-pollutant models. It is possible that fluctuations in PM₁₀ and the other gaseous pollutants may be more representative of the overall pollution mixture than the fluctuations of O₃ levels in this data set.

Although effect estimates for most pollutants were not sensitive to detrending, CO effect estimates were generally larger for the detrended data, as compared with the raw pollutant variable. Because raw CO decreased over time, which was not apparent for the other pollutants considered, this decreasing trend in the CO series may have influenced the pollutant/mortality association such that the effect estimate for raw CO may be attenuated compared with that for detrended CO. It is therefore possible that longer term seasonal influences could have an impact on the observed effect estimates when the raw pollutant is used in the model.

Collectively, the results of this study suggest that older individuals with nonrespiratory primary causes of death (e.g., cardiac deaths) are particularly susceptible to the adverse effects of air pollution when coexisting respiratory conditions are also present. This suggests that past studies may have underestimated the role of respiratory disease in pollution-related mortality and that respiratory disease can have an important contributing role in explaining observed associations between air pollution and nonrespiratory primary causes of death, such as cardiac deaths.

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